Prurigo nodularis

Epidemiology and clinical features

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Learning objectives
After completing this learning activity participants should be able to describe patient populations commonly affected by prurigo nodularis and recognize clinical signs and symptoms of prurigo nodularis, as well as associated co-morbid conditions.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by intensely pruritic, hyperkeratotic nodules that favor the extensor surfaces of the extremities and the trunk. In addition to its significant impact on quality of life, many patients with PN are recalcitrant to therapy because there are currently no therapies approved by the US Food and Drug Administration. In the first article of this 2-part continuing medical education series, we describe the broader epidemiology, patient demographics, physical examination findings, and symptoms to aid in the timely recognition and diagnosis of PN. Furthermore, we quantify the burden of comorbidities in PN by discussing the broad spectrum of systemic diseases and mental health conditions that have been associated with this condition. The second article of this 2-part series focuses on the pathogenesis of PN and provides detailed algorithms for comprehensive work-up and management. (J Am Acad Dermatol 2020;83:1559-65.)

Key words: clinical features; comorbidities; epidemiology; itch; physical examination; prurigo nodularis; pruritus; symptoms.

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CLINICAL FEATURES OF PRURIGO NODULARIS

Key points

- Prurigo nodularis is a chronic, pruritic inflammatory skin disease characterized by numerous symmetrically distributed hyperkeratotic nodules most commonly on the extensor surfaces of the extremities and trunk
- Prurigo nodularis is diagnosed clinically, although biopsy specimens of lesional skin can show thickened, hyperplastic dermal nerve fibers with decreased density of intraepidermal nerve fibers

Prurigo nodularis (PN) was first described by Hyde in 1909,[1] who detailed the hyperkeratotic nodules and intractable pruritus experienced by patients with this chronic dermatosis. With no targeted therapies approved by the US Food and Drug Administration available to date and many patients refractory to off-label treatments, PN exerts a significant burden on quality of life.[2-4] Increased rates of mental health conditions including depression and anxiety have been reported in PN, as well as various systemic comorbidities that will be discussed later.[5,6] Whether these conditions contribute directly to PN or are the result of a shared systemic process that also causes the skin lesions of PN is not known.

The number of nodules in PN can range from several to >100, and they are often grouped and symmetrically distributed on the extensor surfaces of the extremities and trunk (Fig 1). Nodules can affect any area of the body, although patients typically display the "butterfly sign" where skin on the upper aspect of the back is spared.[7] Most lesions of PN measure between several millimeters up to 2 cm in diameter. Accompanying excoriation and crusting are common secondary signs of an intractable itch–scratch cycle, with pruritus so severe in some patients that bleeding can also result (Fig 2).[8] While the skin between nodules is often normal, it can also be dry, lichenified, or show signs of postinflammatory pigmentary changes.[9] Pruritus is a necessary feature in PN, although some patients may also have burning or stinging pain.[10]

To date, PN remains a clinical diagnosis.[4,7] Though not necessary for diagnosis, skin biopsy specimens of nodules in PN often show thickened, hyperplastic dermal nerve fibers along with decreased density of intraepidermal nerve fibers.[3,9] In addition, PN has also been associated with peripheral neuropathies in an epidemiologic study.[11] However, recent studies suggest that intraepidermal structural alterations may be the result of mechanical damage from chronic scratching.[12] Updates in the literature regarding the pathogenesis of PN will be discussed in the second article in this continuing medical education series.

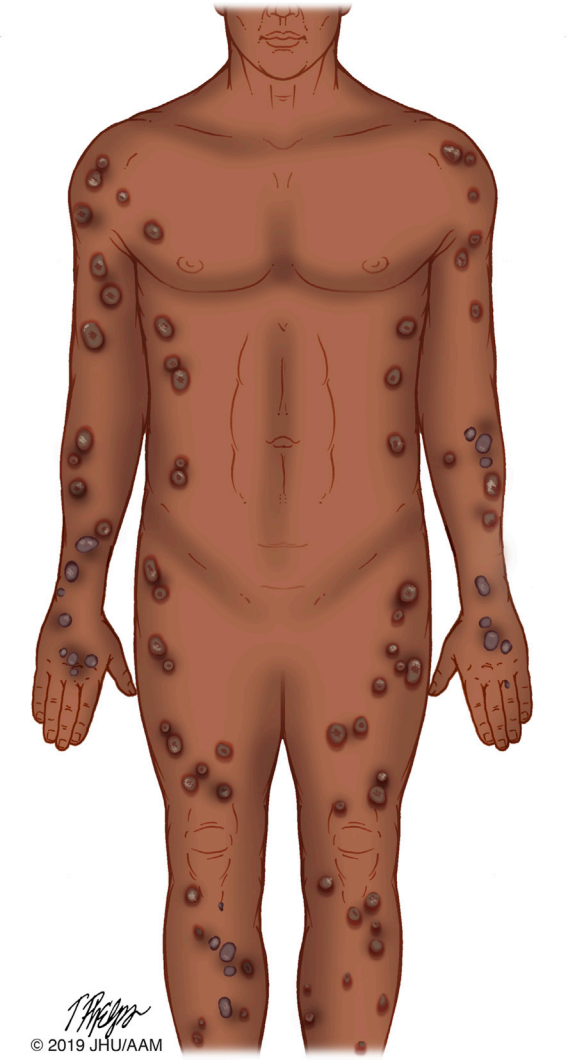

Fig 1. Prurigo nodularis clinical presentation. Figure courtesy of Tim Phelps © 2019 JHU AAM, Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine.

PATIENT DEMOGRAPHICS AND EPIDEMIOLOGY

Key points

- Prurigo nodularis most commonly affects middle-aged adults and tends to be diagnosed more frequently in females compared with males
- Patients with skin of color, including African Americans, are also at increased risk

Prevalence

PN is a relatively rare condition, with an estimated prevalence of 72 per 100,000 individuals in an epidemiologic study of US adults 18 to 64 years of

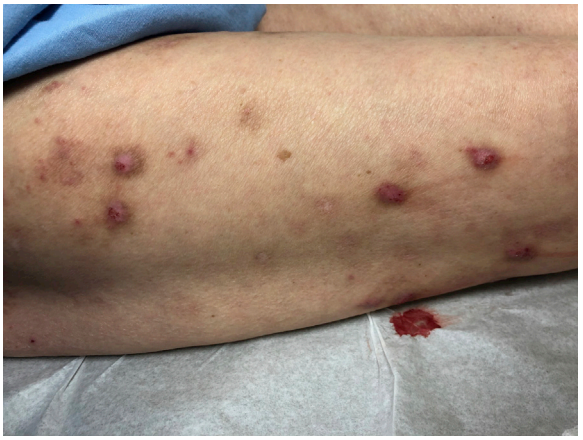

Fig 2. Clinical photograph of prurigo nodularis. Intense itching experienced by patients can perpetuate the chronic itch–scratch cycle and lead to bleeding from excoriations.

age who have health care insurance.[13] Given the variability in the coding of PN in medical claims data, this figure may be a conservative estimate. More research is needed quantify the prevalence of PN in the pediatric population and in adults ≥65 years of age.

Age

The mean and median ages of patients with PN (N = 7095) identified in the epidemiologic study were 50.9 and 54 years, respectively.[13] A separate study conducted at a single institution in the United States found that among 909 patients with PN the relative majority was between 51 and 65 years of age.[14] Analysis of the National Inpatient Sample 2016 dataset found that the mean age of patients hospitalized with PN was 55.2 years.[15] Although PN is a condition that most commonly affects middle-aged adults in the fifth and sixth decades of life, small case series have also reported PN in pediatric patients and in older adults.[16,17]

Gender

PN was first characterized in a cohort of exclusively female patients in the early 20th century.[1] While clinical experience since then has shown that PN affects both genders, there is some evidence that PN is slightly more common in females. In an epidemiologic study of 7095 adult patients with PN in the United States, 53.1% were female while 46.9% were male.[13] In addition, there may also be differences in the gender distribution of PN by race. A single-center study found that 54.6% of African American patients with PN were female compared with 50.5% of whites with PN and 41.9% of Asians with PN.[14] Further research is needed to elucidate any gender differences in PN and how race may serve as an effect modifier.

Race

Both single-institution and national database research suggests that PN is more common in patients with skin of color. Boozalis et al[14] reported a 3.4-fold increased odds (95% confidence interval [CI] 2.9-3.9, $P < .001$) of PN in African Americans compared with whites in the ambulatory and inpatient setting.[14] Analysis of the National Inpatient Sample 2016 data also showed increased odds of patients hospitalized with PN being black (odds ratio [OR] 4.43, $P < .001$), Asian (OR 3.44, $P = .003$), or Hispanic (OR 1.77, $P = .02$) respectively, compared with being white.[15] In addition to being at higher risk for PN, patients with atopic dermatitis who are African American can present with more numerous PN lesions compared with other racial groups.[18] Barriers to access and suboptimal care for atopic dermatitis in African American patients may contribute to a higher prevalence of moderate-to-severe atopic dermatitis and increase the risk of concomitant PN in this population.[19] Recognizing the disproportionate burden of PN in patients with skin of color may help mitigate disparities in health outcomes for these patients.

Health care setting

Analysis of patients with PN who were hospitalized in 2016 showed that these patients were more likely to have Medicare (OR 2.81, $P < .001$) or Medicaid (OR 2.24, $P < .001$) compared with private insurance.[15] Furthermore, patients with PN were more likely to receive care at teaching hospitals (OR 2.60, $P < .001$) compared with nonteaching hospitals.

Other demographic variables

In an analysis of insurance claims data from 2016-2017, regional distribution (eg, Northeast, North Central, South, and West) and industry of employment of patients with PN were similar to age- and sex-matched control subjects.[13]

ASSOCIATED COMORBID CONDITIONS

Key points

- Prurigo nodularis is associated with increased rates of mental health, endocrine, cardiovascular, and renal disorders, as well as HIV and malignancy
- The burden of systemic comorbidities in prurigo nodularis often exceeds that of other inflammatory skin disorders (ie, atopic dermatitis or psoriasis)

A variety of comorbidities associated with PN have been identified through case series and

epidemiologic studies. Knowledge of associated comorbidities can help guide the provider in the comprehensive work-up and management of patients with PN.

Mental health

PN is associated with an increased rate of psychiatric conditions, including anxiety and depression.[20] A Danish study of 877 patients with PN identified from the national registry demonstrated increased odds of depression (adjusted OR 2.82 [95% CI 2.14-3.72]) and anxiety (adjusted OR 2.06 [95% CI 1.23-3.44]) compared with age- and sex-matched control subjects.[5] The depression and anxiety experienced by patients with PN are often severe enough to warrant pharmaceutical intervention, with increased use of both antidepressants (adjusted OR 2.60 [95% CI 2.24-3.01]) and anxiolytics (adjusted OR 4.64 [95% CI 3.97-5.43]) in PN compared with matched control subjects. No statistically significant difference in the rate of completed suicides was seen in patients with PN compared with control subjects.

Corroborating the Danish study, an epidemiologic study using health care claims within the United States of 7095 adults with PN showed increased rates of mood (OR 2.24 [95% CI 2.05-2.46]) and anxiety (OR 1.93 [95% CI 1.78-2.09]) disorders compared with age- and sex-matched control subjects.[13] Furthermore, odds of mood and anxiety disorders were also increased in patients with PN compared with those with other inflammatory skin disorders (ie, atopic dermatitis and psoriasis, respectively).

While several studies have examined anxiety and depression in patients with PN, fewer studies have examined other mental health disorders in patients with PN. However, a large US epidemiologic study also found significantly increased odds of eating disorders, self-harm, attention-deficit/hyperactivity disorder, and schizophrenia in patients with PN compared with age- and sex-matched control subjects.[13] Many of these mental health conditions (eg, psychotic, mood, and substance use disorders) have also been reported in lichen simplex chronicus, a condition similarly characterized by intense pruritus and scratching.[21] One study of patients with PN/lichen simplex chronicus using the National Inpatient Sample database found increased rates of hospitalization for mental health concerns as well as longer inpatient stays in this population.[21] Given the scarcity of clinical data confirming these epidemiologic associations, more research is needed to quantify the full burden of mental health conditions in the PN population. Whether mental health conditions contribute to disease pathogenesis in PN or become exacerbated by chronic symptoms of intense refractory pruritus also deserve further study.[22]

Infectious

PN has been associated with multiple infectious agents, among which HIV has been particularly well-studied.[23-26] Although patients with HIV are affected by a variety of chronic pruritic dermatoses, PN in particular has been associated with severe itch and significantly lower quality of life in this population.[23] In a US-based study, patients with PN had 2.68 higher odds (95% CI 1.66-4.33) of HIV infection compared with age- and sex-matched control subjects. In areas with high endemic levels of HIV infection, such as French Guyana, PN has also been noted to have a high positive predictive value of 72% for poorly controlled HIV and advanced immunosuppression (ie, CD4 count <200 cells/mm^3).[23,24] Interestingly, lesions of PN in HIV-infected individuals may be responsive to treatment of HIV with antiretroviral therapy (ie, raltegravir).[26,27] The successful use of immunomodulatory agents such as thalidomide for treatment of patients with PN both with and without HIV further suggests the important role of the immune response in PN.[28] In addition, thalidomide's established anxiolytic properties may augment its efficacy for treatment of PN given the significant burden of mental health comorbidities experienced by these patients.[29]

Apart from HIV, PN has also been associated with other viral infections, including hepatitis C in clinical case series.[30-32] Although the relationship between hepatitis C infection and PN has yet to be demonstrated on a larger epidemiologic level, it has been hypothesized that immunologic dysregulation and circulating immune complexes in the context of persistent hepatitis C virus infection may also be implicated in the pathogenesis of PN.[31,32]

Autoimmune and autoinflammatory

Patients with PN have been reported to have increased rates of celiac disease and thyroid disease (eg, Hashimoto thyroiditis).[33-35] An epidemiologic study from the United States corroborated an increased odds of celiac disease in patients with PN compared with control subjects (OR 2.70 [95% CI 1.43-5.08]) but also implicated other conditions, including inflammatory bowel diseases and type 1 diabetes mellitus.[13] Patients with PN had an increased odds of Crohn's disease (OR 2.40 [95% CI 1.51-3.81]), ulcerative colitis (OR 1.64 [95% CI 1.13-2.37]), and type 1 diabetes mellitus (OR 2.23 [95% CI 1.72-2.90]). Given the hypothesized influence of the immune response in PN pathogenesis discussed earlier in the infectious comorbidity section, more

research is needed to understand the link between autoimmune/autoinflammatory processes and PN.

Dermatologic and allergic

The presence of other dermatologic diseases is common in PN, with the majority of patients with PN also affected by another skin condition.[17,36] Among dermatologic conditions associated with PN, atopic dermatitis has been the most widely reported in both case series and epidemiologic studies.[2,14,18] The prevalence of atopic dermatitis in patients with PN has been increased compared with control subjects, with evidence that patients with PN may also be more likely to have an atopic disposition.[2,37] In line with this hypothesis, a large-scale epidemiologic study in the United States also found increased odds of allergic comorbidities including asthma and urticaria in patients with PN compared with age- and sex-matched controls.[13]

In addition to atopic dermatitis, other dermatologic conditions have also been associated with PN. One epidemiologic study demonstrated over 4 times increased odds of psoriasis and over 70 times increased odds of neurotic excoriations in patients with PN compared with matched control subjects.[13] Case reports and series have also highlighted other skin diseases associated with PN, including keratoacanthomas, bullous pemphigoid, and linear immunoglobulin A disease.[38-41]

Malignancies

PN has also been documented arising in association with cancer, most notably hematologic malignancies such as non-Hodgkin and Hodgkin lymphoma.[42-44] Not only can PN be the presenting symptom of lymphoma, treatment of the underlying lymphoma can lead to improvement or resolution of PN lesions in some patients.[42,43] Compared with control subjects, patients with PN had a 2-5 times increased odds of non-Hodgkin lymphoma according to 2 US-based epidemiologic studies.[13,45] In addition, PN has also been linked to primary cutaneous lymphoma, mycosis fungoides, and multiple myeloma.[45,46]

With regard to solid tumors, patients with PN may have increased odds of some cancers such as those of the gastrointestinal tract.[45,47] However, additional research is needed to verify these associations in large, multi-institutional studies.

Endocrine

Endocrine and metabolic dysfunction are common in patients with PN, affecting over half of patients with PN in some cohorts.[2,48] The association of PN with type 1 and 2 diabetes mellitus has been particularly notable.[2,14,18,48] Compared with matched control subjects, patients with PN had a 2.23 times increased odds (95% CI 1.72-2.90) of type 1 diabetes mellitus and a 1.42 times increased odds (95% CI 1.30-1.55) of type 2 diabetes mellitus.[13] In addition, increased odds of hypertension, hyperlipidemia, and obesity have been shown in patients with PN relative to control subjects from the general population.[13,14] It has been hypothesized that pruritus caused by underlying metabolic dysregulation may contribute to the development of PN, although this process is still not well understood.[48]

Other systemic diseases

Finally, PN has been also been associated with additional systemic diseases that involve various organ systems including renal, hematologic, pulmonary, and cardiovascular.

The association of PN with kidney dysfunction, especially end-stage renal disease, is consistent throughout the published literature.[49-51] Although less common than anemia in terms of absolute prevalence, chronic kidney disease was found to be increased in patients with PN in 2 separate epidemiologic studies conducted in the United States.[13,14] Compared with age- and sex-matched control subjects, patients with PN had a 1.85 times increased odds of chronic kidney disease (95% CI 1.52-2.25) and a 4.88 times increased odds of requiring dialysis (95% CI 2.40-9.92).[13] Increased pruritus experienced by patients with chronic kidney disease caused by increased systemic inflammation, metabolic/electrolyte dysregulation, and neuropathic abnormalities may increase the risk of PN in this population.[52,53]

Anemia, most commonly iron deficiency anemia, has been reported in both case reports and small case series of patients with PN.[54,55] In the latter, the reported prevalence of anemia in patients with PN has been as high as 27.5%.[17,36] However, a more recent epidemiologic study has not reported a statistically significant odds of anemia in PN compared with matched control subjects (OR 1.37 [95% CI 0.93-2.03]).[13] Whether anemia is independently linked with PN deserves further investigation because patients with PN are also more likely to have conditions that increase risk of anemia (eg, renal failure, as discussed previously).

In addition, chronic obstructive pulmonary disease may be more common among patients with PN compared with the general population.[13,14] Although data on tobacco use and smoking in patients with PN are lacking, further investigation into this modifiable risk factor for chronic obstructive pulmonary disease is key.

Finally, there is evidence of increased cardiovascular and cerebrovascular disease in patients with PN. Compared with age- and sex-matched control subjects, patients with PN had roughly double the odds of heart failure, cerebrovascular disease, and coronary heart disease according to one epidemiologic study.[13] Moreover, the odds of cerebrovascular and coronary heart disease in patients with PN was increased even compared with patients with psoriasis after adjusting for age and sex. This is notable because patients with psoriasis are known to have an increased risk of atherosclerotic conditions (including cerebrovascular and coronary heart disease) that are linked to increased mortality compared with the general population.[56] The heavy burden of comorbidities in PN even compared to other inflammatory skin disorders such as psoriasis highlights the need for epidemiologic evaluation of mortality in patients with PN.

In conclusion, it is notable that despite the diverse range of comorbidities in PN many of them share an association with chronic pruritus. Although the etiology of PN is still under active investigation, chronic itch in the setting of these conditions (eg, atopic dermatitis, HIV, end-stage renal disease, Hodgkin lymphoma, and others) may promote and perpetuate the itch–scratch cycle that is central to PN. This is supported by data showing an increased prevalence of PN in populations with poor control of pruritic conditions, such as in African Americans who have higher rates of moderate-to-severe atopic dermatitis. Given that not all patients with chronic pruritus will develop PN and that some patients with PN do not have an identifiable underlying cause, the pathogenesis of disease is likely multifactorial and influenced by individual patient characteristics. Key areas of future research include understanding how the severity and duration of chronic pruritus may affect the development of PN and exploring the causal links between PN and associated comorbidities.

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Answers to CME examination

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1. b
2. c
3. b
4. e